UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,618	09/19/2008	Antonio Cattaneo	AbdnByClnt-Cattaneo94250	5926

20311 7590 08/24/2010

LUCAS & MERCANTI, LLP
475 PARK AVENUE SOUTH
15TH FLOOR
NEW YORK, NY 10016

EXAMINER	
NOAKES, SUZANNE MARIE	
ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
08/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/583,618	CATTANEO ET AL.	
	Examiner	Art Unit	
	SUZANNE M. NOAKES	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 8-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/17/2010; 09/13/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The location and Examiner assigned to your application at the US Patent Office has changed. Please direct all further correspondence to AU1656 and the examiner signed below.

Election/Restrictions

2. Applicant's election without traverse of Group I, claims 1, 2 and 24 in the reply filed on 01 July 2010 is acknowledged. With regard to Applicants "election of species" for sequences SEQ ID NOs: 37 and 38, the current Examiner does not see where this was imposed in the previous Office action on pp. 3 or 4; however, if said Examiner has overlooked such a requirement, it is noted that it is hereby withdrawn as there is no search burden.

Status of Claims

3. Claims 1, 2 and 8-24 are pending. Claims 8-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Claims 1, 2 and 24 are subject to examination the merits.

Priority

4. Applicants claim to foreign priority document filed in Italy (RM2003000601) on 24 December 2003 is acknowledged.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 17 March 2010 and 13 September 2007 have been considered by the examiner. See initialed and signed PTO-1449's.

Drawings

6. It is noted that the Brief Description of the Drawings makes reference to colored drawings. However, Applicants have not: i) filed a petition under 37 C.F.R. 1.84(a)(2) or 1.84(b)(2) requesting entry of color photographs or drawings into the application, ii) submitted three sets of color drawings or color photographs, iii) paid the appropriate fee AND iv) amended the specification to include the following language as the first paragraph of the Brief Description of the Drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Should Applicants want the noted Figures to be in color, the above four steps need to be complied with. If, on the other hand, Applicants do not wish to submit color photographs, Applicants are required to amend the specification to remove reference to color drawings in the appropriate sections of the Brief Description of the Drawings.

Specification

7. The specification is objected to because there is no heading for the "Brief Description of the Drawings" section of the application.

Claim Objections

8. Claims 1, 2 and 24 are objected to because of the following informalities: the claims can be improved with respect to form and clarity - it seems that the claims are direct translations from Italian and could be improved considerably.

For instance, the clause in step (b) might be more appropriate as a wherein clause at the end of the sentence.

Also, as an example, the "frameworks acceptors" would be better as 'framework acceptors'.

In addition, in part c), it would be clearer to refer that the structural comparison between the VH and VL variable regions of the animal antibody obtained in (a) and the regions VH and VL obtained in (b). ** It is noted, however, that these regions are not stated as being obtained in step (b) as the claim is currently written.

These are just a few examples of the grammatical inconsistencies and awkwardness of the claims that arise from what appears to a direct translation.

Appropriate corrections are required.

Claim Rejections - 35 USC § 112 – 2nd paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 2 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is a method of *humanizing* the VH and VL regions of an animal antibody - that is, one skilled in the art inserts human sequences/regions *into* the animal antibody. However, the last step of claim 1 states it is the other way around, e.g. inserting in appropriate positions the sequence of animal antibodies *into* the human sequences or human antibodies, which results in doing the opposite of what the preamble suggests.

Adding to the confusion is the definition in the specification which states "The term "humanized immunoglobulin" refers to an immunoglobulin which comprises a human framework and at least one CDR deriving from a non human antibody and in which each constant region present is substantially identical to a region of human immunoglobulin (at least 85%, preferably at least 90-95% identical). Hence, all the parts of a humanized immunoglobulin except the CDR are substantially identical to the corresponding regions of one or more sequences of natural human immunoglobulins."

In light of this discrepancy, the Examiner will interpret the claims as defined in the specification and as known in the art, e.g. the humanization of an antibody is done by using a human antibody frame work and inserting animal CDR regions into said antibody (rather than the humanizing the VH and VL regions of an animal antibody as stated in the preamble).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1, 2 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Queen et al. in view of Ramslund et al. (J. Mol Regocnition, 2002, 15:248-259 - cited on IDS of 09/13/2007).

Queen et al. (U.S. Pat. No. 5,693,761) discloses a method of humanizing antibodies based on the premise that ascribes avidity loss to problems in the structural motifs in the humanized framework which, because of steric or other chemical incompatibility, interfere with the folding of the CDRs into the binding-capable conformation found in the mouse antibody. To address this problem, Queen teaches using human framework sequences closely homologous in linear peptide sequence to framework sequences of the mouse antibody to be humanized. Accordingly, the methods of Queen focus on comparing framework sequences between species. Typically, all available human variable domain sequences are compared to a particular mouse sequence and the percentage identity between correspondent framework residues is calculated. The human variable domain with the highest percentage is selected to provide the framework sequences for the humanizing project. Queen also teaches that it is important to retain in the humanized framework, certain amino acid residues from the mouse framework critical for supporting the CDRs in a binding-

capable conformation. Potential criticality is assessed from molecular models. Candidate residues for retention are typically those adjacent in linear sequence to a CDR or physically within 6 Å of any CDR residue.

Queen et al., however, do not teach that the molecular models are have been determined crystallographically.

Ramsland et al. teach the comparison of crystal structures of humanized and mouse-human chimeric Fab antibodies (resolution 2.6Å). It is noted that in 2002 (the time of publication) there were more than 300 crystallographically determined antibody structures determined and found in the protein databank (PDB), 50 of those are different human Immunoglobulins (see Introduction). Crystallographic structures were obtained from the PDB with resolution limits of 2.6Å or better and/or a *R*-cryst of 21% ensuring high quality structural comparisons (See Table 1, p. 254). These comparisons allowed the identification of amino acids residues in the acceptor framework regions which could be retro-mutated to the corresponding donor framework region to restore the shape of the binding site in the acceptor antibody (see pg.255, 2nd col., last paragraph to pg.256 1st col., 1st paragraph and Figure 6). Ramslund et al. conclude that comparison of the three dimensional crystal structures allows the identification of structural differences for antibody engineering, especially in the development of humanized antibodies (see Conclusion, pg.256 2nd col., last paragraph, to pg.257).

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Queen et al. method by utilizing crystallographic structures of antibodies as taught in Ramslund et al. in the process rather than

molecular models. One skilled in the art would be motivated to make such a substitution because the crystallographic models are seen as a more accurate and true reflection of the antibodies which are concerned and to be humanized and thus will likely produce better results. One skilled in the art furthermore would have a reasonable expectation of success in doing so because Ramslund et al. teaches that upon comparing crystallographic structures, residues that need to be changed and were not expected to necessarily need changing could be identified by the structural comparisons.

Therefore when the references are taken together, the instant claims are deemed as *prima facie* obvious.

13. Claims 1, 2 and 24 rejected under 35 U.S.C. 103(a) as being unpatentable over Pedersen et al. (US 5,639,641) in view of Ramsland et al. (J. Mol Regocnition, 2002, 15:248-259 - cited on IDS of 09/13/2007).

Pedersen et al. teach humanizing a rodent antibody (Ab) or fragment by resurfacing said antibody wherein the method comprises:

(a) determination of the conformational structure of the variable region of the rodent Ab or fragment by constructing a 3D model of the rodent Ab variable region;

(b) generating sequence alignments from relative accessibility distributions from X-ray crystallographic structures of the rodent Ab variable region heavy and light chains to give a set of heavy and light chain framework positions;

(c) defining a set of heavy and light chain surface exposed amino acid residues using the set of framework positions generated in (b);

(d) identifying from human antibody amino acid sequences a set of heavy and light chain surface exposed amino acid residues that is most closely identical to the set of residues defined in (c);

(e) substituting the set of heavy and light chain surface exposed amino acid residues defined in (c) with the set of residues identified in (d);

(f) constructing a 3D model of the rodent antibody variable region resulting from the substitution of (e);

(g) identifying any amino acid residues from the set identified in (d), that are within 5 Å of any atom of any residue of the complementarity determine regions (CDRs) of the rodent Ab to be humanized ; and

(h) changing/retro-mutating any residue identified in (g) from the human to the original rodent amino acid residue.

It is noted that step (a) need not be conducted first, but must be conducted prior to step (g).

Pedersen et al., however, do not teach the method wherein the rodent antibody molecular model has been determined crystallographically either *ab initio* or alternatively obtained from the protein databank (PDB).

Ramsland et al. teach the comparison of crystal structures of humanized and mouse-human chimeric Fab antibodies (resolution 2.6Å). It is noted that in 2002 (the time of publication) there were more than 300 crystallographically determined antibody

structures determined and found in the protein databank (PDB), 50 of those are different human Immunoglobulins (see Introduction). Crystallographic structures were obtained from the PDB with resolution limits of 2.6Å or better and/or a *R*-cryst of 21% ensuring high quality structural comparisons (See Table 1, p. 254). These comparisons allowed the identification of amino acids residues in the acceptor framework regions which could be retro-mutated to the corresponding donor framework region to restore the shape of the binding site in the acceptor antibody (see pg.255, 2nd col., last paragraph to pg.256 1st col., 1st paragraph and Figure 6). Ramslund et al. conclude that comparison of the three dimensional crystal structures allows the identification of structural differences for antibody engineering, especially in the development of humanized antibodies (see Conclusion, pg.256 2nd col., last paragraph, to pg.257).

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Pedersen et al. method by utilizing crystallographic structures as the starting models for rat antibodes as taught in Ramslund et al. in the process rather than molecular models. As noted by Ramslund et al., there were 300 antibody crystallographic structures found within the PDB at the time of publication and thus a variety of starting models could be chosen. One skilled in the art would be motivated to make such a substitution because the crystallographic models are seen as a more accurate and true reflection of the antibodies which are concerned and to be humanized and thus will likely produce better results. One skilled in the art furthermore would have a reasonable expectation of success in doing so because Ramslund et al. teaches that upon comparing crystallographic structures, residues that

need to be changed and were not expected to necessarily need changing could be identified by the structural comparisons.

Therefore when the references are taken together, the instant claims are deemed as *prima facie* obvious.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1, 2 and 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 24 of copending Application No. 12/838,062. Although the conflicting claims are not identical, they are not patentably distinct from each other because the two claims sets are identical except for the instant claims are drawn to a genus of any or all animal anibodies used in the methods, whereas the '062 application is drawn to the specific antibody anti-NGF. This, however, is notably a preferred embodiment of the instant application and as such, the claims overlap in scope to such an extent that they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

References of Interest – Not Relied Upon

16. Tamura et al (2000) Structural correlates of an anti-carcinoma antibody: identification of specificity-determining residues (SDRs) and development of a minimally immunogenic antibody variant by retention of SDRs only. J. Immunol. 164:1432-1441. This reference has the premise that increasing the proportion of characteristically

human sequence in a humanized antibody will reduce that antibody's immunogenicity, and accordingly disclose methods for grafting partial CDR sequences. Determination of the three-dimensional structure of antibody-antigen complexes showed that many residue positions assigned to the CDRs defined by Kabat and Wu rarely were directly involved in antigen binding.

17. Harris et al. (EP 0 578 515 A2 – cited on IDS of 03/17/2010).

Harris et al. teach producing a humanized monoclonal antibody (MAb) by utilising a process of comparative model building by utilizing known 3-D structures as determined crystallographically comprising:

(a) selecting a monoclonal antibody to be humanized, such as a murine antibody;

(b) searching computer databanks for protein crystal structures demonstrating more than 50% sequence homology to the variable region of said antibody to produce a structural template;

(c) determining the structure of the CDR region loops and assigning the loops to cononical loop conformations;

(d) determining the framework (F) residues crucial to CDR loop conformation;

(e) replacing the CDR loops of structural templates with cononical CDR backbone templates using interactive computer graphics;

(f) searching computer databanks to extract initial backbone approximations (e.g. root–mean-square deviations (RMS)) for each loop for non-cononical loops;

(g) replacing non-conserved amino-acid side chains in similar positions on the antibody and on the computer model with human residues using interactive computer graphics to produce a model having a combination of backbone fragments of different antibodies with replaced side chains;

(h) solvating the models with a water layer corresponding to approx. 7Å;

(i) refining the structure with an energy minimization protocol to produce a structure wherein all atoms of the system are freely mobile;

(j) searching computer databanks to find homologous human sequences for the variable light and variable heavy chains;

(k) combining the sequences in (j) to obtain human templates;

(l) comparing the structural template of (a) with the human templates of (k) and selecting a human template with variable regions having more than 50% sequence identity with the structural template;

(m) determining the CDR loops of the human template selected in (l);

(n) replacing the CDR loop region of the selected human template with the analogous sequences from the antibody to produce a phase I humanized sequence;

(o) superimposing the Ab models and phase I humanized sequence to compare binding site regions;

(p) identifying by the comparision in (o), all amino acids in the framework residues and CDR junction residues which interact with the antibody CDR loops that can be important to structural integrity of the antibody binding sites (ABS);

(q) reinserting into the phase I humanized sequence all residues identified in (p) to be different from those in the Ab, and refining the resultant structure with an energy minimisation protocol, to produce a phase II humanized sequence;

(r) refining the phase II humanized sequence using interactive conformational search protocols on all regions of the ABS and by analysis of the ABS to determined which regions of the CDR surface or CDR-framework region are not likely to involve antigen (Ag) binding; and

(s) replacing (e.g. retromutating) the residues in the non-antigen binding regions of the ABS with residues corresponding to human residues, to produce a humanized MAb. (see claims 1 and 2 and pp. 4-6).

It is noted that backbone comparisons of initial structures should RMS deviations of less that 3Å (see Example 1, p. 10-11).

Conclusion

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUZANNE M. NOAKES whose telephone number is (571)272-2924. The examiner can normally be reached on 7.00 AM-3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SUZANNE M. NOAKES/
Primary Examiner, Art Unit 1656
17 August 2010